

REMARKS

Claims 1-7 are pending in the instant application. Claims 1-7 have been rejected. Claims 6 and 7 have been objected to. Claims 1 and 3 have been cancelled. Claims 2, 4-7 have been amended. Support for these amendments can be found in the specification.

New Claims 8 and 9 have been added. No new matter has been added. Support for the new Claims 8 and 9 can be found in the specification, specifically on pages 10-15.

Objection to Claims 6 and 7

The Examiner has rejected Claim 6 for having an improper dependent form. Applicants have amended the instant claim in order to provide the correct form for a dependent claim. In light of this amendment, this objection should be rendered moot.

The Examiner has rejected Claim 7 for the informality of reciting the term "stomach cancer" twice. Applicants have amended the instant claim to remove the extraneous term. In light of this amendment, this objection should be rendered moot. Accordingly, Applicants respectfully request the objections to Claims 6-7, be withdrawn.

Rejection of Claim 7 under 35 USC §112, first paragraph

The Examiner rejected Claim 7 under 35 U.S.C. 112, first paragraph for allegedly failing to enable a person skilled in the art to make and use the invention. Specifically, the Examiner asserts that:

The specification does not contain sufficient disclosure to allow one skilled in the art to "practice the invention commensurate in scope with the breath of the claims." The specification does not meet the enablement requirement when undue experimentation is required to practice the invention. The MPEP states that several factors should be considered to determine if the disclosure satisfies the enablement requirement. The factors to be considered are the (1) breadth of the claim, (2) level of one of ordinary skill, (3) amount of direction provided by the inventor (4) existence of working examples, (6) level of predictability, and (7) quantity of experimentation needed to make or use the invention (MPEP 2164.01(a)).

In the instant application, the Examiner states that although the specification enables a person skilled in the art to utilize this method for treatment of colon cancer, stomach cancer, lung cancer and leukemia, it does not provide sufficient enablement for the treatment of all the cancers listed in the claim. The Examiner states that due to the low level of predictability in the art, absent guidance, one of ordinary skill would not expect that anti-tumor effect of the compounds on stomach and lung cancer cells would correlate to anti-tumor effects on all the cancers listed in the instant claim. The Examiner contends that a person skilled in the art would recognize that it is highly unlikely that a single compound would treat an array of cancers as specified in the instant claim.

The Applicants respectfully traverse the rejection of Claim 7.

The Examiner notes that the use of a single chemical agent for the treatment (and prevention) of an array of cancers has not been previously reported. The Examiner alleges that no single chemical compound has been found useful in the treatment of all types of a particular cancer.

Applicants respectfully note that 70% of the types of cervical cancer itself are now known to be prevented by the cancer vaccine GardasilTM, which is 100% effective in preventing those types of cancer.

Indolopyrrolocarbazole derivatives of various structural classes have been shown to inhibit cell proliferation in at least 6 human tumor cell lines of the following types: gastric (MKN-45), lung (PC-13, LX-1), breast (MX-1), and colon (DLD-1, LS180). In addition, a mouse tumor line (P388, leukemia) was also growth inhibited in the presence of indolopyrrolocarbazole compounds. See U.S. Patent No. 6,703,373.

Applicants respectfully contend that the claims of the present invention encompass a limited number of compounds. The claimed compounds have a high degree of structural similarity. More specifically, each of the compounds is an indolopyrrolocarbazole.

Applicants submit that, given the limited number of compounds encompassed by the claims of the instant invention, the structural similarity between the claimed compound, the potent *in vitro* and *in vivo* inhibitory effect of the claimed compounds on broad array of tumor cell lines, these test results fully support the claims directed towards the treatment of cancer.

Applicants maintain that the Examiner has not made a *prima facie* case of nonenablement, and in light of the argument presented, it is not reasonable to conclude that

the Applicant has not enabled the claims. Accordingly, Applicants respectfully request the rejection of Claims 3, 4, and 7 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection of Claim 5 and 7 under 35 U.S.C. §112, second paragraph

The Examiner rejected Claims 5 and 7 under 35 U.S.C. §112, second paragraph for allegedly being indefinite and failing to point out and distinctly claim the subject matter which the Applicants regard as the invention. Specifically, the Examiner indicated that Claims 5 and 7 do not end with a period, therefore it is unclear if the claims end as recited or if additional text is intended. Applicants have amended Claim 5 and 7 to add a period to the ends of these claims. In light of these amendments, this rejection should be rendered moot. Accordingly, Applicants respectfully request the rejection of claims 5 and 7 under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejection of Claims 1-7 under Obviousness-type Double Patenting

The Examiner provisionally rejected Claims 1-7 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 copending Application No. 10/509,061 ('061 application) and claims 1-8 of copending Application No. 10/571,861 ('861 application). As this rejection is a provisional rejection, based on pending applications which are still undergoing prosecution and wherein no allowable subject matter has yet been identified, Applicants respectfully request that this rejection be held in abeyance.

The Examiner has rejected Claims 1-7 under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,703,373 ('373 patent) and claims 1-5 of U.S. Patent No. 5,591,842 ('842 patent). Specifically the Examiner asserts that:

The instant invention, although not identical to the aforementioned patents, are not patentably distinct from each other, because both disclose indolopyrrolocarbazole derivatives and teach the use of the compounds as antitumor agents. The instant application discloses indolopyrrolocarbazole derivatives with the same core structure as the '842 patent, however the '842 patent does not disclose the specific structure comprising the C1-3 alkyl group attached to nitrogen on one side and to an unsubstituted pyridyl, furyl, or thienyl on the other side. Similarly, '373 patent discloses indolopyrrolocarbazole derivatives with the same core structure as the instant

invention. However the '373 patent discloses a 1-3C alkyl group between an exocyclic nitrogen and R, which comprises of both unsubstituted and substituted pyridyl, furyl, and thienyl.

The Examiner asserts one skilled in the art would find the instant compounds obvious in light of the aforementioned patents. It is common practice in pharmaceuticals to test compounds which are suitable for use as a medicament. "Where prior art compound essentially brackets the claimed compounds and are well known anticancer/antitumor agents, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new anticancer/antitumor agents." *In re Payne*, 203 USPQ 245, 254-255 (C.C.P.A. 1979). Therefore one skilled in the art would find the instantly claimed compounds to be obvious based on the disclosures set forth in '842 and '373 patents.

Without conceding the correctness of the Examiner's argument, but to advance the prosecution of the instant application, Applicants have cancelled Claims 1 and 3. In light of these cancellations, the rejection of Claims 1 and 3 should be rendered moot.

However, Applicants respectfully traverse the rejections of Claims 2 and 4-7.

An obviousness-type double patenting rejection is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103", therefore the analysis should parallel the guidelines for a 35 U.S.C. 103 determination. MPEP 804 (citing *In re Braithwaite*, 154 USPQ 29 (CCPA 1967)).

In the Case of *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992), the Federal Circuit Court of Appeals held that a novel ammonium salt of a known herbicidal compound was patentable despite the prior publication of the genus of ammonium salts of the compound and a specific discussion of certain of them. The court took the view that the prior publication was of a "potentially infinite genus" of such ammonium salts and held that the compound claimed was not sufficiently similar in structure of the prior art to render it *prima facie* obvious.

Applicants submit that an analogous situation applies in the instant case. Applicants respectfully note that the '373 patent generically teaches a variety of indolopyrrolocarbazole compounds, including C1-3 alkyl between an exocyclic nitrogen and both substituted and unsubstituted pyridyl, furyl, or thienyl groups. One compound, having a pyridin-4-yl methyl moiety on the exocyclic amine, is disclosed in the '373 patent, but the

specific potency of that compound in comparison to the other "substituted" heterocycle containing compounds is not disclosed. The '842 patent teaches a variety of indolopyrrolocarbazole compounds without a C1-3 alkyl bridge between the exocyclic nitrogen and 5- or 6-member heterocycles. In contrast, the instant application teaches a select class of indolopyrrolocarbazole derivatives with both a C1-3 alkyl bridge and only the unsubstituted aforementioned heterocycles. The '373 and '842 patents do not provide motivation to one of ordinary skill in the art to make the compounds claimed in the instant application.

Applicants maintain that given that the compounds claimed in the instant application is not rendered obvious in light of the '373 and '842 patents, the instant application does not constitute an unjustified or improper timewise extension of the right to exclude. Accordingly, Applicants respectfully request the rejection of Claims 1-7 on the ground of nonstatutory obviousness-type double patenting be withdrawn.

Rejection of Claims 1-7 under 35 U.S.C. §103(a)

The Examiner rejected Claims 1-7 under 35 U.S.C. §103(a) as allegedly being obvious over Kojiri et al. (U.S. Patent 5,591,842 ('842 patent) and U.S. Patent ('373 patent)). Specifically the Examiner asserts that:

The instant application discloses indolopyrrolocarbazole derivatives with the same core structure as the '842 patent, however the '842 patent does not disclose the specific structure comprising the C1-3 alkyl group attached to nitrogen on one side and to an unsubstituted pyridyl, furyl, or thienyl on the other side. Similarly, '373 patent discloses indolopyrrolocarbazole derivatives with the same core structure as the instant invention. However the '373 patent discloses a 1-3C alkyl group between an exocyclic nitrogen and R, which comprises of both unsubstituted and substituted pyridyl, furyl, and thienyl. Both '373 patent and '842 patent teach the use of the compounds as antitumor agents.

The Examiner asserts one skilled in the art would find the instant compounds obvious in light of the aforementioned patents. It is common practice in pharmaceuticals to test compounds which are suitable for use as a medicament. "Where prior art compound essentially brackets the claimed compounds and are well known anticancer/antitumor agents, one of ordinary

skill in the art would be motivated to make the claimed compounds in searching for new anticancer/antitumor agents." *In re Payne*, 203 USPQ 245, 254-255 (C.C.P.A. 1979). Therefore one skilled in the art would be find the instantly claimed compounds to be obvious based on the disclosures set forth in '842 and '373 patents.

Without conceding the correctness of the Examiner's argument, but to advance the prosecution of the instant application, Applicants have cancelled Claims 1 and 3. In light of these cancellations, the rejection of Claims 1 and 3 should be render moot.

However, Applicants respectfully traverse the rejections of Claims 2 and 4-7. The reasons for traversal are analogous to those provided in response to the obviousness-type double patenting rejections.

In the Case of *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992), the Federal Circuit Court of Appeals held that a novel ammonium salt of a known herbicidal compound was patentable despite the prior publication of the genus of ammonium salts of the compound and a specific discussion of certain of them. The court took the view that the prior publication was of a "potentially infinite genus" of such ammonium salts and held that the compound claimed was not sufficiently similar in structure of the prior art to render it *prima facie* obvious.

Applicants submit that an analogous situation applies in the instant case. Applicants respectfully note that the '373 patent generically teaches a variety of indolopyrrolocarbazole compounds, including C1-3 alkyl between an exocyclic nitrogen and both substituted and unsubstituted pyridyl, furyl, or thienyl groups. The '842 patent teaches a variety of indolopyrrolocarbazole compounds without a C1-3 alkyl bridge between the exocyclic nitrogen and 5- or 6-member heterocycles. In contrast, the instant application teaches a select class of indolopyrrolocarbazole derivatives with both a C1-3 alkyl bridge and only the unsubstituted aforementioned heterocycles. The '373 and '842 patents do not provide motivation to one of ordinary skill in the art to make the compounds claimed in the instant application.

Therefore, one skilled in the art would not consider the instant application obvious based on the evidence that the select class of compounds instantly claimed exhibit significantly greater inhibitory effects on tumor growth than the indolopyrrolocarbazole derivatives disclosed in the '373 and '842 patents. Accordingly, Applicant respectfully request the rejection of Claims 1-7 under 35 U.S.C. §103(a), be withdrawn.

The Applicants additionally maintain that the species claimed in the instant invention are patentably distinct from the generic claims taught in the '373 patent. Many of the examples in the '373 patent are directed to substituted pyridyl, furyl and thienyl groups, unlike the instant application, which only generically claims unsubstituted furyl and thienyl groups. Applicants note that the species claims (new claims 8 and 9) are directed to compounds having unsubstituted theinyl, furyl, 3-pyridyl and 2-pyridyl heterocyclic groups. The best mode section of the disclosure lists the preferred embodiments as the aforementioned heterocycles substituted with alkoxy groups having 1-4 carbon atoms (See pg. 3, line 10-15 of specification). The vast majority of the compounds specifically disclosed in the '373 patent featured a substituted pyridyl, furyl, or thienyl groups (See pg. 9-28).

Applicants further note that the first disclosure of the subject matter of the '373 patent was upon publication of the issued US patent, which occurred after the earliest priority date of the instant application. Applicants therefore respectfully contend that the '373 patent is not effective prior art against the instant application under §103(a).

If a telephonic communication with the Applicants' representative will advance the prosecution of the instant application, please telephone the representative indicated below. Applicants believe no additional fees are due but the Commissioner is authorized to charge any fees required in connection with this amendment to Merck Deposit Account No. 13-2755.

Respectfully submitted,

By: 

David A. Muthard
Registration No. 35,297
Attorney for Applicants

Merck & Co., Inc.
PO Box 2000 - RY 60-30
Rahway, New Jersey 07065-0907
Telephone No.: (732) 594-3903
Facsimile No.: (732) 594-4720

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